Ciba Specialty Chemicals
North America

8EHQ-0802-15180
MR 60966

8EHP-02-15180

88020000166

Ciba

August 5, 2002

Via Federal Express
Confidential

US Environmental Protection Agency
OPPT Document Control Office Mail Code 7407M
Attention: Section 8(e) Submission
EPA East Building, Room 6428
1201 Constitution Avenue NW
Washington, DC 20460-0001

SANITIZED COPY

RECEIVED
OPPT NCIC
2002 AUG 29 AM 10: 07

Subject: TSCA 8(e) Notice - CGX RU 997 (TKA 40254)

Dear Section 8(e) Coordinator:

This letter contains Confidential Business Information. Confidential Information bracketed { }.

In accordance with EPA's March 16, 1978 Policy Statement on Section 8(e) reporting under the Toxic Substances Control Act (TSCA), the EPA's June, 1991 TSCA Section 8(e) Reporting Guide, Ciba Specialty Chemicals Corporation wishes to bring to the attention of the Environmental Protection Agency the results observed in a contact hypersensitivity test with an experimental elastomers antioxidant, CGX RU 997. CGX RU 997 is a {

RECEIVED
OPPT CBIC
02 AUG -6 PM 3:30

3

{ }

Please note that a CASRN has not been assigned to this product.

A contact hypersensitivity maximization-test was conducted in albino Guinea pigs with CGX RU 997 (OECD Guideline 406). Ten of ten (10/10) animals of the test group showed a positive skin response after the challenge procedure. All animals showed erythema at the treatment site; no toxic symptoms were evident. In accordance to the allergenic potency grading pursuant to Magnusson and Kligman, the test item is considered to be an extreme sensitizer.

SANITIZED COPY

COMPANY SANITIZED

540 White Plains Road
Tarrytown, New York 10591

Tel. 914-785-4311
Fax 914-785-4147

We are enclosing a copy of the study ***"TKA 40254 (CGX RU 997) Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test"*** RCC,Ltd, CH-4452, Itingen, Switzerland; RCC Study Number 841900

Based upon current EPA guidelines, it is felt these results warrant reporting under TSCA 8(e). A sanitized copy of this letter and study reports are also enclosed. A Confidential Business Information Substantiation for this product is also submitted pursuant to TSCA 8(e) requirements. Please call the undersigned if you have any questions concerning this submittal.

Respectfully,
Ciba Specialty Chemicals Corporation

Thomas Barber
Manager, Product Compliance

RCC Study Number 841900

TKA 40254 (CGX RU 997):

Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test

Report

Author: G. Arcelin

Sponsor: Ciba Specialty Chemicals Inc.
CH-4002 Basel / Switzerland

6/7/02

SANITIZED
COPY

RCC

Table of contents

1 PREFACE 5
1.1 GENERAL 5
1.2 RESPONSIBILITIES 5
1.3 SCHEDULE 5
1.4 ARCHIVING 6
1.5 SIGNATURE PAGE 7
1.6 QUALITY ASSURANCE UNIT 8
1.7 STATEMENT OF COMPLIANCE 9
1.8 CERTIFICATION OF GLP AND VERIFICATION OF THE REPORT 10
1.9 ACCREDITATION 11
1.10 TEST GUIDELINES 11
1.11 REFERENCES 11
2 SUMMARY 12
3 PURPOSE 14
4 MATERIALS AND METHODS 14
4.1 TEST SYSTEM 14
4.2 ALLOCATION 15
4.3 HUSBANDRY 15
4.4 TEST ITEM 16
4.5 VEHICLE 16
4.6 AUXILIARY COMPOUNDS 17
4.7 TEST ITEM PREPARATION 17
4.8 RATIONALE 18
4.9 READINGS AND SCORING 18
4.10 SELECTION OF CONCENTRATION OF TEST ITEM FOR MAIN STUDY 18
5 STUDY CONDUCT - TREATMENT PROCEDURE 19
5.1 PRETEST PERFORMED WITH TKA 40254 (CGX RU 997) BEFORE AND DURING THE ACCLIMATIZATION PERIOD OF THE CONTROL AND TEST GROUP 19
5.2 MAIN STUDY 20
5.2.1 INDUCTION 20
5.2.1.1 INTRADERMAL INJECTIONS / PERFORMED ON TEST DAY 1 20
5.2.1.2 EPIDERMAL APPLICATIONS / PERFORMED ON TEST DAY 8 21
5.2.2 CHALLENGE / PERFORMED ON TEST DAY 22 21

Table of contents (cont'd)

5.3 INTERPRETATION 22
5.4 RATING OF ALLERGENICITY ACCORDING TO MAGNUSSON AND KLIGMAN 22
5.5 OBSERVATIONS 22
6 PATHOLOGY 23
6.1 NECROPSY 23
7 STATISTICAL ANALYSIS 23
8 DATA COMPILATION 23
9 RESULTS 24
Main Study 24
9.1 SKIN EFFECTS AFTER INTRADERMAL INDUCTION - PERFORMED ON TEST DAY 1 24
9.2 SKIN EFFECTS AFTER EPIDERMAL INDUCTION - PERFORMED ON TEST DAY 8 24
9.3 SKIN EFFECTS AFTER THE CHALLENGE - PERFORMED ON TEST DAY 22 24
9.4 VIABILITY / MORTALITY / MACROSCOPIC FINDINGS 25
9.5 CLINICAL SIGNS, SYSTEMIC 25
9.6 BODY WEIGHTS 25

Table of contents (cont'd)

APPENDIX A
PRETEST 27
MAIN STUDY
- INDUCTION 29
- CHALLENGE 31

APPENDIX B
NECROPSY
- MACROSCOPIC FINDINGS 36

APPENDIX C
BODY WEIGHTS
- SUMMARY 38
- INDIVIDUAL 41

APPENDIX D
RESULTS OF POSITIVE CONTROL 43

APPENDIX E
SUMMARY TABLE OF STUDY INFORMATION AND RESULTS 53

APPENDIX F
CERTIFICATION
- ACCREDITATION / EUROPEAN STANDARD EN 45001 55
- GLP – CERTIFICATION 56

LAST PAGE OF REPORT 56

1 PREFACE

1.1 GENERAL

Title	TKA 40254 (CGX RU 997): Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test
Sponsor	Ciba Specialty Chemicals Inc. CH-4002 Basel / Switzerland
Study Monitor	Mrs. Isabelle Frei
Test Facility	RCC Ltd Toxicology Division Wölferstrasse 4 CH-4414 Füllinsdorf / Switzerland

1.2 RESPONSIBILITIES

Study Director	G. Arcelin
Deputy for Study Director	M. Ott
Technical Coordinator	P. Reissbrodt
Head of RCC Quality Assurance	I. Wüthrich

1.3 SCHEDULE

Experimental Starting Date	08-JAN-2002
Experimental Completion Date	18-FEB-2002
Delivery of the Animals	08-JAN-2002 (pretest) 15-JAN-2002 (main study)
Pretest Start	08-JAN-2002
Acclimatization (main study)	15-JAN-2002 to 21-JAN-2002
Observation (main study)	15-JAN-2002 to 18-FEB-2002
Treatment (main study)	22-JAN-2002 to 12-FEB-2002
Termination	18-FEB-2002
Study Completion Date	07-JUN-2002

1.4 ARCHIVING

RCC Ltd (CH-4452 Itingen / Switzerland) will retain the study plan, raw data, a sample of test item(s) and the final report of the present study for at least ten years. No data will be discarded without the Sponsor's consent.

1.5 SIGNATURE PAGE

Study Director: G. Arcelin

date: 07-JUN-2002

Management: S. Corney

date: 07-JUN-2002

1.6 QUALITY ASSURANCE UNIT

RCC Ltd, Toxicology Division, CH-4452 Itingen / Switzerland

STATEMENT

RCC STUDY NUMBER : 841900

TEST ITEM : TKA 40254 (CGX RU 997)

STUDY DIRECTOR : G. Arcelin

TITLE : TKA 40254 (CGX RU 997):
Contact Hypersensitivity in Albino Guinea Pigs,
Maximization-Test

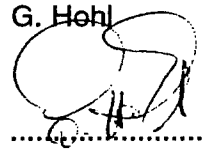
The general facilities and activities are inspected periodically and the results are reported to the responsible person and the management.

Study procedures with exception of the formulation trials were periodically inspected. The study plan and this report were audited by the Quality Assurance Unit. The dates are given below.

Dates and Types of QAU Inspections	Dates of Reports to the Study Director and to Management
19-DEC-2001 Study Plan	19-DEC-2001
22-JAN-2002 Test System / Test Item / Treatment / Raw Data / Dose preparation	22-JAN-2002
04-MAR-2002 to 06-MAR-2002 Report	06-MAR-2002

This statement also confirms that this final report reflects the raw data.

Quality Assurance: G. Hohl



.....
date: 07-JUN-2002

GOOD LABORATORY PRACTICE

1.7 STATEMENT OF COMPLIANCE

RCC STUDY NUMBER	:	841900
TEST ITEM	:	TKA 40254 (CGX RU 997)
STUDY DIRECTOR	:	G. Arcelin
TITLE	:	TKA 40254 (CGX RU 997): Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test

The formulation trials were performed before the study initiation date. Therefore, they are excluded from this statement.

This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted February 2nd, 2000 [RS 813.016.5]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final].

These procedures were consistent with the Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHW, MAFF and MITI).

Study Director: G. Arcelin

G. Arcelin

.....

date: 07 JUN 2002

1.8 CERTIFICATION OF GLP AND VERIFICATION OF THE REPORT

The statement of Compliance with Good Laboratory Practice found in this report, and signed by the Study Director is truthful and accurate, and this report as provided by the test facility is complete and unaltered.

Signature of the Sponsor: .....

.....

Date:

1.9 ACCREDITATION

The test facility "RCC Ltd, Toxicology Division" is accredited according to EN 45001 under accreditation number STS 085 by the Swiss Accreditation Service.

1.10 TEST GUIDELINES

The study procedures described in this report are based on the following guidelines:

Directive 96/54/EEC, B.6. "Acute Toxicity - Skin Sensitization", July 30, 1996.

OECD Guidelines for Testing of Chemicals, Number 406 "Skin Sensitization", adopted by the Council on July 17, 1992 (reported Paris, April 29, 1993).

1.11 REFERENCES

Magnusson, B. and Kligman, A.M., 1969. The Identification of Contact Allergens by Animal Assay. The Guinea Pig Maximization Test. J. Invest. Dermatol. 52: 268-276.

Magnusson, B. and Kligman, A.M., 1970. Allergic contact dermatitis in the guinea pig. Identification of Contact Allergens. Springfield Ill; Charles C Thomas.

2 SUMMARY

In order to assess the cutaneous allergenic potential of TKA 40254 (CGX RU 997), the Maximization-Test was performed in 15 (10 test and 5 control) female albino guinea pigs, in accordance with OECD Guideline No. 406 and the Directive 96/54/EEC, B.6.

The intradermal induction of sensitization in the test group was performed in the nuchal region with a 25 % dilution of the test item in PEG 300 and in an emulsion of Freund's Complete Adjuvant (FCA) / physiological saline. The epidermal induction of sensitization was conducted for 48 hours under occlusion with the undiluted test item one week after the intradermal induction. The animals of the control group were intradermally induced with PEG 300 and FCA/physiological saline and epidermally induced with PEG 300 under occlusion.

Two weeks after epidermal induction the control and test animals were challenged by epidermal application of the test item at 25 % in PEG 300 and PEG 300 alone under occlusive dressing.

Cutaneous reactions were evaluated at 24 and 48 hours after removal of the dressing.

Results

Skin Reactions after the Challenge Procedure

	after 24 hours	after 48 hours
	positive / total % positive of total	positive / total % positive of total
CONTROL GROUP		
TKA 40254 (CGX RU 997) 25 % in PEG 300 (left flank)	0 / 5 0	0 / 5 0
PEG 300 only (right flank)	0 / 5 0	0 / 5 0
TEST GROUP		
TKA 40254 (CGX RU 997) 25 % in PEG 300 (left flank)	10 / 10 100	9 / 9* 100
PEG 300 only (right flank)	0 / 10 0	0 / 9 0

* One animal (no. 330) of the test group was found dead on test day 25 (i.e. 5 hours prior to the 48-hour reading in the challenge phase). At necropsy, no macroscopic findings were noted. The cause of death could not be established. The death was considered to be spontaneous and treatment unrelated.

No toxic symptoms were evident in the guinea pigs of the control or test group.

All test animals showed discrete/patchy to moderate/confluent erythema after the challenge treatment with TKA 40254 (CGX RU 997) at 25 % (w/w) in PEG 300. No skin effect was observed in the control group.

Conclusion

Based on the above mentioned findings in an adjuvant sensitization test (M&K-test) in guinea pigs, TKA 40254 (CGX RU 997) is considered to be an extreme skin sensitizer.

3 PURPOSE

The purpose of this skin sensitization study was to assess the allergenic potential of TKA 40254 (CGX RU 997) when administered to the skin of albino guinea pigs.

This study should provide a rational basis for risk assessment of the sensitizing potential of the test item in man.

The sensitivity and reliability of the experimental technique employed was assessed by use of 2-MERCAPTOBENZOTHIAZOLE which is recommended by the OECD 406 Guidelines and is known to have moderate skin sensitization properties in the guinea pig strain. The results from the most recent test run (RCC study number 905635, performed from 14-MAY-2001 to 21-JUN-2001) are included in this report under the APPENDIX D.

4 MATERIALS AND METHODS

4.1 TEST SYSTEM

Test system	Ibm: GOHI; SPF-quality guinea pigs (synonym: Himalayan spotted)
Rationale	Recognized by the international guidelines as a recommended test system (e.g. OECD, EEC).
Source	RCC Ltd, Biotechnology & Animal Breeding Division, Wölferstrasse 4, CH-4414 Füllinsdorf / Switzerland
Number of animals for main study / pretest	15 females / 3 females (nulliparous and non-pregnant)
Age at pretest start/beginning of acclimatization period	4 - 7 weeks
Body weight at pretest start	Pretest groups: 396 - 417 g
Body weight at beginning of acclimatization period	Control and test group 403 - 447 g
Identification	By unique cage number and corresponding ear tags.
Randomization	Selected by hand at time of delivery. No computer randomization.
Acclimatization	One week for the control and test group under test conditions after health examination. No acclimatization for the animals of the pretest. Only animals without any visible signs of illness were used for the study.

4.2 ALLOCATION

The animals were distributed as follows:

	NUMBER OF ANIMALS PER GROUP	ANIMAL NUMBERS PER GROUP
1 Intradermal Pretest	1	314
2 Epidermal Pretest	2	315 - 316
3 Control Group	5	317 - 321
4 Test Group	10	322 - 331

4.3 HUSBANDRY

Room no.	105 / RCC Ltd, Füllinsdorf
Conditions	**Standard Laboratory Conditions** Air-conditioned with target ranges for room temperature 20 ± 3 °C, relative humidity 30-70 % and approximately 10-15 air changes per hour. Room temperature and humidity were monitored continuously and values outside of these ranges occasionally occurred, usually following room cleaning. These transient variations are considered not to have any influence on the study and, therefore, these data are not reported but are retained at RCC. The animals were provided with an automatically controlled light cycle of 12 hours light and 12 hours dark. Music was played during the daytime light period.
Accommodation	Individually in Makrolon type-4 cages with standard softwood bedding ("Lignocel", Schill AG, CH-4132 Muttenz).
Diet	Pelleted standard Provimi Kliba 3418, batch no. 93/01, guinea pig breeding / maintenance diet, containing Vitamin C (Provimi Kliba AG, CH-4303 Kaiseraugst), *ad libitum*. Results of analyses for contaminants are archived at RCC Ltd, Itingen.
Water	Community tap water from Füllinsdorf, *ad libitum*. Results of bacteriological, chemical and contaminant analyses are archived at RCC Ltd, Itingen.

4.4 TEST ITEM

The following information was provided by the sponsor:

Identification	TKA 40254
Product name	CGX RU 997
Description	liquid
Batch number	02/2001
Purity	see Analytical Certificate (Ciba Specialty Chemicals Inc.; Study No. 14019814-1)
Stability of test item	Stable under storage conditions; expiration date: 31-AUG-2002
Stability of test item dilution	Stable in polyethylene glycol 300 and in a 1:1 (v/v) mixture of FCA/physiological saline for at least 2 hours at room temperature (determined at RCC Ltd, Environmental Chemistry & Pharmanalytics Division, under RCC project number 841913).
Storage conditions	In the original container, at room temperature (range of 20 ± 3 °C), away from direct sunlight.
Safety precautions	Routine hygienic procedures were used to ensure the health and safety of the personnel.

4.5 VEHICLE

The following information was provided by RCC Ltd:

Identification	Polyethylene glycol 300 (PEG 300)
Description	colorless viscous liquid
Lot number	424718/1 42701
Source	FLUKA Chemie GmbH, CH-9471 Buchs
Stability of vehicle	Stable under storage conditions; expiration date: 10-AUG-2002
Storage conditions	In the original container, at room temperature (range of 20 ± 3 °C), away from direct sunlight.
Safety precautions	Routine hygienic procedures were used to ensure the health and safety of the personnel.

The vehicle was selected based on preliminary solubility testing which was performed before the study initiation date. Therefore, the formulation trials were excluded from the statement of GLP compliance. The test item was not soluble in purified water but was readily soluble in PEG 300.

4.6 AUXILIARY COMPOUNDS

The following information was provided by RCC Ltd:

FCA

Identification	Freund's Adjuvant - Complete
Description	clear, amber liquid containing light colored particles
Lot No.	39H8926
Source	Sigma, 3050 Spruce Street, Saint Louis, Missouri 63103 USA
Purity	each ml contains 1 mg Mycobacterium Tuberculosis (H 37Ra, ATCC 25177), heat killed and dried, 0.85 ml mineral oil and 0.15 ml mannide monooleate
Expiry date	23-MAY-2002
Storage conditions	In the original container, in the refrigerator (range of 5 ± 3 °C), away from direct sunlight.

Physiological saline

Identification	Natrium chloratum 0.9 %
Description	colorless liquid
Charge No.	720504/2
Source	G. Streuli & Co. AG, CH-8730 Uznach/Switzerland
Expiry date	July 2004
Storage conditions	In the original container, in the refrigerator (range of 5 ± 3 °C), away from direct sunlight.

4.7 TEST ITEM PREPARATION

The test item and vehicle* or auxiliary compound were placed into a glass beaker on a tared Mettler PM 460 balance and a weight by weight dilution was prepared. Homogeneity of the test item preparation was ensured and maintained during treatment using a magnetic stirrer and/or spatula. The preparations were made immediately prior to each dosing.

Dose levels were in terms of material as supplied by the sponsor.

---

* PEG 300 was used for the intradermal and epidermal pretests. It was also used for the intradermal and epidermal induction and the challenge in the main study. The 1:1 mixture (v/v) of Freund's Complete Adjuvant:physiological saline was used for the pretest and the intradermal induction in the main study.

4.8 RATIONALE

The application procedure was used to detect a possible allergenic potential of the test item applied.

4.9 READINGS AND SCORING

The scoring system was performed by visual scoring of erythema, oedema and other clinical changes of skin conditions. They were assessed using the following Magnusson and Kligman grading scale:

0 = no visible change
1 = discrete or patchy erythema
2 = moderate and confluent erythema
3 = intense erythema and swelling

Grading of all animals was done by positioning the animal under true-light (Philips TLD 36W/84 or Osram 36W/31 830).

4.10 SELECTION OF CONCENTRATION OF TEST ITEM FOR MAIN STUDY

Intradermal and Epidermal Induction:

The concentration of test item used for each induction exposure was well-tolerated systemically and was the highest to cause mild skin irritation.

Epidermal Challenge:

Concentration that was the maximum tested non-irritant concentration.

To determine the different concentrations an intradermal and epidermal pretest was performed as described below.

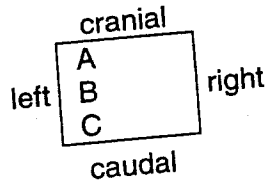
5 STUDY CONDUCT - TREATMENT PROCEDURE

5.1 PRETEST PERFORMED WITH TKA 40254 (CGX RU 997) BEFORE AND DURING THE ACCLIMATIZATION PERIOD OF THE CONTROL AND TEST GROUP

The test item concentrations described below were selected during a preliminary solubility testing which was not inspected by the Quality Assurance Unit.

INTRADERMAL INJECTIONS:

Four intradermal injections (0.1 ml/site) of a 1:1 (v/v) mixture of Freund's Complete Adjuvant/physiological saline were made into the shaved neck of one guinea pig (no. 314). One week later intradermal injections (0.1 ml/site) were made into the clipped flank of the same guinea pig at concentrations of A = 25 %, B = 15 % and C = 10 % of the test item in PEG 300.



Dermal reactions were assessed 24 hours later.

Based on the results, the test item concentration of 25 % was selected for intradermal induction in the main study.

The skin reactions are listed on page 27 in APPENDIX A.

EPIDERMAL APPLICATIONS:

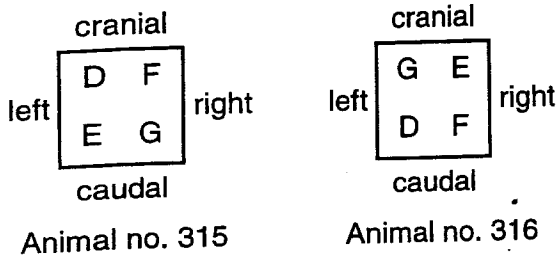
Four intradermal injections (0.1 ml/site) of a 1:1 (v/v) mixture of Freund's Complete Adjuvant/physiological saline were made into the shaved neck of two guinea pigs. One week later both flanks of each of the guinea pigs were clipped and shaved just prior to the application. Thereafter 4 patches of filter paper (3 x 3 cm) were saturated with the test item at D = 100 %, E = 75 %, F = 50 % and G = 25 % and applied to the clipped and shaved flanks. PEG 300 was used for the dilutions. The amount of test item preparation applied was approximately 0.2 g for the test item at 100 % and 75 % and a volume of approximately 0.2 ml was applied for the remaining test item concentrations. The patches were covered by a strip of aluminum foil and firmly secured by elastic plaster wrapped around the trunk and covered with impervious adhesive tape. This procedure ensured the intensive contact of the test item. The dressings were removed after an exposure period of 24 hours.

Twenty-one hours after removal of the dressing the application site was depilated with an approved depilatory cream (VEET Cream, Reckitt & Colman AG, CH-4123 Allschwil) in order to visualize any resulting erythema.

The depilatory cream was placed on the patch sites and surrounding areas, and left on for 3-5 minutes. It was then thoroughly washed off with a stream of warm, running water. Thereafter, the animals were dried with a disposable towel, and returned to their cages.

The reaction sites were assessed 24 and 48 hours after removal of the bandage for erythema and oedema according to the method of Magnusson and Kligman (see 4.9).

The position of the epidermal applications is shown below:



The allocation of the different test item dilutions to the sites (D, E, F, G) on the two animals was alternated in order to minimize site-to-site variation in responsiveness.

Results are listed on page 28 in APPENDIX A. Based on the results obtained the concentration selected for induction and challenge in the main study was 100 % and 25 %, respectively.

5.2 MAIN STUDY

5.2.1 INDUCTION

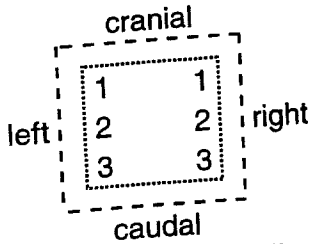
5.2.1.1 INTRADERMAL INJECTIONS / PERFORMED ON TEST DAY 1

An area of dorsal skin from the scapular region (approximately 6 x 8 cm) was clipped free of hair. Three pairs of intradermal injections (0.1 ml/site) were made at the border of a 4 x 6 cm area in the clipped region as follows:

Test Group:
1) 1:1 (v/v) mixture of Freund's Complete Adjuvant and physiological saline.
2) The test item, at 25 % in PEG 300.
3) The test item at 25 % in a 1:1 (v/v) mixture of Freund's Complete Adjuvant and physiological saline.

Control Group:
1) 1:1 (v/v) mixture of Freund's Complete Adjuvant and physiological saline.
2) PEG 300
3) 1:1 (w/w) mixture of PEG 300 in a 1:1 (v/v) mixture of Freund's Complete Adjuvant and physiological saline.

The positions of the intradermal injections are shown below:



- - - - - - - - - - - - - - clipped area
..... area in which injections were made

5.2.1.2 EPIDERMAL APPLICATIONS / PERFORMED ON TEST DAY 8

One week after the injections, the scapular area (approximately 6 x 8 cm) was again clipped and shaved free of hair prior to the application. A 2 x 4 cm patch of filter paper was saturated with the undiluted test item and placed over the injection sites of the test animals. The amount of test item preparation applied was approximately 0.3 g. The patch was covered with aluminum foil and firmly secured by an elastic plaster wrapped around the trunk of the animal and secured with impervious adhesive tape. The occlusive dressings were left in place for 48 hours. The epidermal application procedure described ensured intensive contact of the test item.

The guinea pigs of the control group were treated as described above with PEG 300 only, applied at a volume of approximately 0.3 ml.

The reaction sites were assessed 24 and 48 hours after removal of the bandage for erythema and oedema according to the method of Magnusson and Kligman (see 4.9).

The skin reactions are listed in Tables 1 to 2 in APPENDIX A.

5.2.2 CHALLENGE / PERFORMED ON TEST DAY 22

The test and control guinea pigs were challenged two weeks after the epidermal induction application and were treated in the same way.

Hair was clipped and shaved from a 5 x 5 cm area on the left and right flank of each guinea pig just prior to the application. Two patches (3 x 3 cm) of filter paper were saturated with the test item at the highest tested non-irritating concentration of 25 % (applied to the left flank) and the vehicle only (PEG 300 applied to the right flank) using the same method as for the epidermal application. The volume of test item preparation and vehicle applied was approximately 0.2 ml. The dressings were left in place for 24 hours.

Twenty-one hours after removal of the dressing the test sites treated with the test item were depilated as described in the epidermal pretest.

The reaction sites were assessed 24 and 48 hours after removal of the bandage for erythema and oedema according to the method of Magnusson and Kligman (see 4.9).

The skin reactions are listed in Tables 3 to 6 in APPENDIX A.

5.3 INTERPRETATION

The results obtained from test animals following the challenge application were compared with the results seen in control animals.

An allergic reaction was defined by visible reddening of the challenge site.

If the dermal reactions of test animals following the challenge were more marked and/or persistent than those of the control animals, the animals were considered to show evidence of contact hypersensitivity.

If the dermal reactions of test animals following the challenge were not clearly different from the reactions seen in the control group animals, the results for the test animals were considered "inconclusive".

The test animals were considered to show no evidence of contact hypersensitivity if the dermal reactions to the challenge application were identical or less marked and/or persistent than the reactions observed in the control animals.

By "maximizing" the exposure and enhancing allergenicity, some problems could arise, particularly in relation to specificity, especially the potential for false-positive reactions. An inflammatory response at challenge may not necessarily be due to allergenicity, but instead may be a false-positive irritant response caused by an inducing hyperirritability.

5.4 RATING OF ALLERGENICITY ACCORDING TO MAGNUSSON AND KLIGMAN

Based upon the percentage of animals sensitized (24- and 48-hour reading), the test item was assigned to one of the following five grades of allergenic potency according to Magnusson and Kligman, ranging from weak to extreme:

Sensitization Rate (%)	Grade	Classification
0 - 8	1	weak
9 - 28	2	mild
29 - 64	3	moderate
65 - 80	4	strong
81 - 100	5	extreme

5.5 OBSERVATIONS

The following observations and data were recorded during the study:

Viability / Mortality	Daily from delivery of the animals to the termination of the test.
Clinical signs (systemic)	Daily from delivery of the animals to the termination of the test.

Skin reactions	At the times specified during the pretest, induction and challenge periods.
Body weights	At pretest and acclimatization start, day 1 and termination of the test.

Records were maintained on all additional and standard observations.

6 PATHOLOGY

6.1 NECROPSY

Necropsy was performed in one animal (no. 330) of the test group which was found dead on test day 25 (i.e. 5 hours prior to the 48-hour reading in the challenge phase).

No necropsies were performed in the animals of the control and test group sacrificed at termination of the observation period nor in the animals of the intradermal and epidermal pretest sacrificed on test day 1 of the main study.

The surviving animals were sacrificed by intraperitoneal injection of NARCOREN at a dose of at least 2.0 ml/kg body weight (equivalent to 320 mg sodium pentobarbitone/kg body weight) and discarded.

7 STATISTICAL ANALYSIS

Descriptive statistics (means and standard deviations) were calculated for body weights. No inferential statistics were used.

8 DATA COMPILATION

The following data were recorded on data sheets and transcribed in the report:

skin reactions, viability/mortality and clinical signs.

The following data were compiled into the RCC computer system during recording:

macroscopic findings.

The following data were recorded on-line:

body weights.

9 RESULTS
Main Study

9.1 SKIN EFFECTS AFTER INTRADERMAL INDUCTION - PERFORMED ON TEST DAY 1

The expected and common findings were observed in the control and test group after the different applications using FCA intradermally. These findings consisted of erythema, oedema, necrotizing dermatitis, encrustation, exfoliation of encrustation and also gray discoloration produced by the test item.

No detailed description of the effects is given in the report as these FCA effects are well-known.

9.2 SKIN EFFECTS AFTER EPIDERMAL INDUCTION - PERFORMED ON TEST DAY 8

CONTROL GROUP

No erythematous or oedematous reaction was observed in the animals treated with PEG 300 only.

TEST GROUP

As the undiluted test item stained the skin gray-brown, it was not possible to determine whether erythema was present or not. However, no oedema was observed. The animals were not depilated in the epidermal induction phase.

See Tables 1 and 2, pp. 29 - 30

9.3 SKIN EFFECTS AFTER THE CHALLENGE - PERFORMED ON TEST DAY 22

CONTROL GROUP

No skin reactions were observed in the animals when treated with either PEG 300 only or when treated with the test item at 25 % in PEG 300.

Gray-brown discoloration produced by the test item was noted directly after removal of the patch. To remove the discoloration all animals were depilated 3 hours prior to challenge reading.

See Tables 3 and 4, pp. 31 - 32

TEST GROUP

Discrete/patchy to moderate/confluent erythema were observed in all animals at the 24-hour reading and moderate/confluent erythema was observed in all surviving animals at the 48-hour reading after treatment with the test item at 25 % in PEG 300.

No skin reactions were observed in the animals treated with PEG 300 only.

Gray-brown discoloration produced by the test item was noted directly after removal of the patch. To remove the discoloration all animals were depilated 3 hours prior to challenge reading.

See Tables 5 and 6, pp. 33 - 34

9.4 VIABILITY / MORTALITY / MACROSCOPIC FINDINGS

One animal (no. 330) of the test group was found dead on test day 25 (i.e. 5 hours prior to the 48-hour reading in the challenge phase). At necropsy, no macroscopic findings were noted. The cause of death could not be established. The death was considered to be spontaneous and treatment unrelated.

See p. 36

9.5 CLINICAL SIGNS, SYSTEMIC

No signs of systemic toxicity were observed in the animals.

9.6 BODY WEIGHTS

Animal no. 317 of the control group showed a loss of body weight (20.1 %) between the treatment start and the end of the study.

The body weight of the other animals was within the range commonly recorded for animals of this strain and age.

See pp. 38 - 41

APPENDIX A

PRETEST

MAIN STUDY

- INDUCTION - Epidermal Reactions
- CHALLENGE - Epidermal Reactions

PRETEST

The following reactions were observed in the pretest:

INTRADERMAL INJECTION /
performed before and during the acclimatization period of the control and test group

Vehicle: PEG 300

Animal No.	Sex	Concentration (%)	REACTION READING AFTER 24 HOURS
314	female	25	1
		15	1
		10	1

According to the findings observed, the concentration selected for the main study was 25 %.

PRETEST (CONTINUED)

EPIDERMAL PRETEST /
performed before and during the acclimatization period of the control and test group

Vehicle: PEG 300

Animal No.	Sex	Concentration (%)	REACTION READINGS AFTER REMOVAL OF BANDAGE	
			24 hours	48 hours
315	female	D = 100	1	1
		E = 75	1	1
		F = 50	1	1
		G = 25	0	0
316	female	G = 25	0	0
		D = 100	1	1
		E = 75	1	1
		F = 50	1	1

Three hours prior to the 24-hour reading the test sites were depilated.

According to Magnusson - Kligman and to the findings observed, the undiluted test item was considered to be the tolerated concentration to stimulate a state of immune hypersensitivity and 25 % as the highest tested non-irritating concentration to be used for the challenge.

MAIN STUDY - INDUCTION

TABLE 1 : CONTROL GROUP

SKIN RESPONSE AFTER THE EPIDERMAL APPLICATION OF THE VEHICLE (PEG 300) DURING INDUCTION PERIOD (SCAPULAR AREA)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
317	female	0	0
318	female	0	0
319	female	0	0
320	female	0	0
321	female	0	0

MAIN STUDY - INDUCTION (CONTINUED)

TABLE 2 : TEST GROUP

SKIN RESPONSE AFTER THE EPIDERMAL APPLICATION OF TKA 40254 (CGX RU 997) (100 %) DURING INDUCTION PERIOD (SCAPULAR AREA)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
322	female	-*	-*
323	female	-	-
324	female	-	-
325	female	-	-
326	female	-	-
327	female	-	-
328	female	-	-
329	female	-	-
330	female	-	-
331	female	-	-

* Due to a gray-brown discoloration produced by the test item a possible erythema reaction could not be determined. The animals were not depilated.

MAIN STUDY - CHALLENGE

TABLE 3 : CONTROL GROUP

SKIN RESPONSE AFTER THE CHALLENGE APPLICATION OF PEG 300 (RIGHT FLANK)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
317	female	0	0
318	female	0	0
319	female	0	0
320	female	0	0
321	female	0	0

MAIN STUDY - CHALLENGE (CONTINUED)

TABLE 4 : CONTROL GROUP

SKIN RESPONSE AFTER THE CHALLENGE APPLICATION OF TKA 40254 (CGX RU 997), 25 % IN PEG 300 (LEFT FLANK)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
317	female	0	0
318	female	0	0
319	female	0	0
320	female	0	0
321	female	0	0

Three hours prior to the 24-hour reading of the challenge the test sites were depilated.

MAIN STUDY - CHALLENGE (CONTINUED)

TABLE 5 : TEST GROUP

SKIN RESPONSE AFTER THE CHALLENGE APPLICATION OF PEG 300 (RIGHT FLANK)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
322	female	0	0
323	female	0	0
324	female	0	0
325	female	0	0
326	female	0	0
327	female	0	0
328	female	0	0
329	female	0	0
330	female	0	EXITUS
331	female	0	0

MAIN STUDY - CHALLENGE (CONTINUED)

TABLE 6 : TEST GROUP

SKIN RESPONSE AFTER THE CHALLENGE APPLICATION OF TKA 40254 (CGX RU 997), 25 % IN PEG 300 (LEFT FLANK)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
322	female	1	2
323	female	2	2
324	female	1	2
325	female	2	2
326	female	2	2
327	female	2	2
328	female	1	2
329	female	2	2
330	female	1	EXITUS
331	female	1	2

Three hours prior to the 24-hour reading of the challenge the test sites were depilated.

APPENDIX B

NECROPSY

- MACROSCOPIC FINDINGS

RCC STUDY NUMBER 841900
TKA 40254 (CGX RU 997)

MACROSCOPIC FINDINGS
FEMALES
GROUP 4 (TEST GROUP)

ANIMAL 330 (SPONTANEOUS DEATH, 15-FEB-2002)

NO FINDINGS NOTED

APPENDIX C

BODY WEIGHTS

- SUMMARY

- INDIVIDUAL

RCC STUDY NUMBER 841900
TKA 40254 (CGX RU 997)

BODY WEIGHTS (GRAM) SUMMARY
FEMALES

PRETEST		GROUP 1 INTRADERMAL PRETEST	GROUP 2 EPIDERMAL PRETEST	GROUP 3 CONTROL GROUP
DAY 1	MEAN	417	401	---
WEEK 1	ST.DEV.	---	7.1	---
	MINIMUM	417	396	---
	MAXIMUM	417	406	---
	N	1	2	0

	GROUP 4 TEST GROUP
MEAN	---
ST.DEV.	---
MINIMUM	---
MAXIMUM	---
N	0

RCC STUDY NUMBER 841900
TKA 40254 (CGX RU 997)

BODY WEIGHTS (GRAM) SUMMARY
FEMALES

ACCLIMATIZATION		GROUP 1 INTRADERMAL PRETEST	GROUP 2 EPIDERMAL PRETEST	GROUP 3 CONTROL GROUP
DAY 1 WEEK 1	MEAN	404	407	435
	ST.DEV.	---	19.5	4.0
	MINIMUM	404	394	431
	MAXIMUM	404	421	442
	N	1	2	5

	GROUP 4 TEST GROUP
MEAN	425
ST.DEV.	12.3
MINIMUM	403
MAXIMUM	447
N	10

RCC STUDY NUMBER 841900
TKA 40254 (CGX RU 997)

BODY WEIGHTS (GRAM) SUMMARY
FEMALES

TREATMENT		GROUP 1 INTRADERMAL PRETEST	GROUP 2 EPIDERMAL PRETEST	GROUP 3 CONTROL GROUP	GROUP 4 TEST GROUP
DAY 1 WEEK 1	MEAN	422	421	475	459
	ST.DEV.	---	15.6	22.4	13.9
	MINIMUM	422	410	452	443
	MAXIMUM	422	432	503	480
	N	1	2	5	10

		GROUP 1 INTRADERMAL PRETEST	GROUP 2 EPIDERMAL PRETEST	GROUP 3 CONTROL GROUP	GROUP 4 TEST GROUP
DAY 28 WEEK 4	MEAN	---	---	517	569
	ST.DEV.	---	---	91.5	38.9
	MINIMUM	---	---	365	498
	MAXIMUM	---	---	609	619
	N	0	0	5	9

BODY WEIGHTS (GRAM)
FEMALES

	PRETEST	ACCLIMATIZATION	TREATMENT	
DAYS	1	1	1	28
WEEKS	1	1	1	4
ANIMAL				
GROUP 1 (INTRADERMAL PRETEST)				
314	417	404	422	---
GROUP 2 (EPIDERMAL PRETEST)				
315	396	394	410	---
316	406	421	432	---
GROUP 3 (CONTROL GROUP)				
317	---	433	457	365
318	---	431	468	516
319	---	435	452	555
320	---	436	503	609
321	---	442	493	538
GROUP 4 (TEST GROUP)				
322	---	432	444	563
323	---	420	452	530
324	---	437	480	592
325	---	403	443	498
326	---	447	469	586
327	---	421	467	619
328	---	425	466	597
329	---	430	475	594
330	---	420	443	---
331	---	414	452	542

APPENDIX D

RESULTS OF POSITIVE CONTROL

RCC Study Number 905635

2-MERCAPTOBENZOTHIAZOLE:

Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test

POSITIVE CONTROL

performed from 14-MAY-2001 to 21-JUN-2001

RESULTS OF POSITIVE CONTROL (CONTINUED)

1 SUMMARY

For validation of sensitivity of the Maximization-Test of B. Magnusson and A.M. Kligman (1969) as well as the sensitivity of the test system used, a known sensitizer 2-MERCAPTOBENZOTHIAZOLE was selected as a positive control. This was performed in accordance with the recommendation of the OECD for testing of chemicals number 406 "Skin Sensitization Test", adopted by the Council on July 17, 1992 (reported Paris, April 29, 1993).

The raw data from this project are kept in a separate file at RCC Ltd. The test described was performed under GLP-conditions with a final QA-check.

The study was performed with 15 (10 test and 5 control) male albino guinea pigs (GOHI), delivered by RCC Ltd, Biotechnology & Animal Breeding Division (CH-4414 Füllinsdorf / Switzerland).

The intradermal induction of sensitization in the test group was performed in the nuchal region with a 5 % dilution of the test item in mineral oil and in an emulsion of Freund's Complete Adjuvant (FCA) / physiological saline. The epidermal induction of sensitization was conducted for 48 hours under occlusion with the test item at 50 % in mineral oil one week after the intradermal induction. The animals of the control group were intradermally induced with mineral oil and FCA/physiological saline and epidermally induced with mineral oil under occlusion. Two weeks after epidermal induction the control and test animals were challenged by epidermal application of the test item at 0.5 % in mineral oil and mineral oil alone under occlusive dressing.

Cutaneous reactions were evaluated at 24 and 48 hours after removal of the dressing.

RESULTS OF POSITIVE CONTROL (CONTINUED)

Results

Skin Reactions after the Challenge Procedure

	after 24 hours positive / total % positive of total	after 48 hours positive / total % positive of total
CONTROL GROUP		
2-MERCAPTOBENZOTHIAZOLE, 0.5 % in mineral oil (left flank)	0 / 5 0	0 / 5 0
Mineral oil only (right flank)	0 / 5 0	0 / 5 0
TEST GROUP		
2-MERCAPTOBENZOTHIAZOLE, 0.5 % in mineral oil (left flank)	10 / 10 100	10 / 10 100
Mineral oil only (right flank)	0 / 10 0	0 / 10 0

No toxic symptoms were evident in the guinea pigs of the control or test group.

No deaths occurred.

All 10 test animals showed discrete/patchy to intense erythema and swelling at the 24- and 48-hour reading after the challenge treatment with 2-MERCAPTOBENZOTHIAZOLE at 0.5 % (w/w) in mineral oil.

No skin effect was observed in the control group.

2 CONCLUSION

Based on the above mentioned findings in an adjuvant sensitization test (M&K-test) in guinea pigs and in accordance to Commission Directive 96/54/EEC, 2-MERCAPTOBENZO-THIAZOLE does have to be classified and labelled as a skin sensitizer.

RESULTS OF POSITIVE CONTROL (CONTINUED)

3 TEST ITEM

Identification	2-MERCAPTOBENZOTHIAZOLE
Description	Solid
Date of test item receipt	26-MAR-2001
Batch number	10315HU-120
Purity	98 %
Stability of test item	Stable under storage conditions; expiration date: 26-MAR-2002
Stability of test item dilution	Stable in mineral oil for at least 22 hours (determined at RCC Ltd, Environmental Chemistry & Pharmanalytics Division, RCC project 905488, non GLP, is excluded from the statement of compliance).
Storage conditions	In the original container, at room temperature (range of 20 ± 3 °C), away from direct sunlight.
Safety precautions	Routine hygienic procedures were used to ensure the health and safety of the personnel.

4 VEHICLE

Identification	Mineral oil
Description	viscous liquid
Lot number	119H0221
Source	Sigma, 3050 Spruce Street, Saint Louis, Missouri 63103 USA
Stability of vehicle	Stable under storage conditions; expiration date: 02-APR-2006
Storage conditions	In the original container, at room temperature (range of 20 ± 3 °C), away from direct sunlight.
Safety precautions	Routine hygienic procedures were used to ensure the health and safety of the personnel.

RESULTS OF POSITIVE CONTROL (CONTINUED)

5 AUXILIARY COMPOUNDS

FCA

Identification	Freund's Adjuvant - Complete
Description	clear, amber liquid containing light colored particles
Batch No.	20K8933
Source	Sigma, 3050 Spruce Street, Saint Louis, Missouri 63103 USA
Purity	each ml contains 1 mg Mycobacterium Tuberculosis (H 37Ra, ATCC 25177), heat killed and dried, 0.85 ml mineral oil and 0.15 ml mannide monooleate
Expiry date	06-DEC-2001
Storage conditions	In the original container, in the refrigerator (range of 4 ± 3 °C), away from direct sunlight.

Physiological saline

Identification	Natrium chloratum 0.9 %
Description	colorless liquid
Batch No.	805904/1
Source	G. Streuli & Co. AG, CH-8730 Uznach/Switzerland
Expiry date	December 2004
Storage conditions	In the original container, in the refrigerator (range of 4 ± 3 °C), away from direct sunlight.

RESULTS OF POSITIVE CONTROL (CONTINUED)

6 RESULTS OF THE MAIN STUDY – CHALLENGE

TABLE 1: CONTROL GROUP

SKIN RESPONSE AFTER THE CHALLENGE APPLICATION OF MINERAL OIL (RIGHT FLANK)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
39	male	0	0
40	male	0	0
41	male	0	0
42	male	0	0
43	male	0	0

RESULTS OF POSITIVE CONTROL (CONTINUED)

TABLE 2: CONTROL GROUP

SKIN RESPONSE AFTER THE CHALLENGE APPLICATION OF 2-MERCAPTO-BENZOTHIAZOLE, 0.5 % IN MINERAL OIL (LEFT FLANK)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
39	male	0	0
40	male	0	0
41	male	0	0
42	male	0	0
43	male	0	0

Three hours prior to the 24-hour reading of the challenge the test sites were depilated.

RESULTS OF POSITIVE CONTROL (CONTINUED)

TABLE 3: TEST GROUP

SKIN RESPONSE AFTER THE CHALLENGE APPLICATION OF MINERAL OIL (RIGHT FLANK)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
44	male	0	0
45	male	0	0
46	male	0	0
47	male	0	0
48	male	0	0
49	male	0	0
50	male	0	0
51	male	0	0
52	male	0	0
53	male	0	0

RESULTS OF POSITIVE CONTROL (CONTINUED)

TABLE 4: TEST GROUP

SKIN RESPONSE AFTER THE CHALLENGE APPLICATION OF 2-MERCAPTO-BENZOTHIAZOLE, 0.5 % IN MINERAL OIL (LEFT FLANK)

Animal No.	Sex	REACTION READINGS AFTER REMOVAL OF BANDAGE	
		24 hours	48 hours
44	male	1	2
45	male	2	2
46	male	2	2
47	male	1	1
48	male	2	2
49	male	3	3
50	male	3	3
51	male	2	2
52	male	1	2
53	male	2	3

Three hours prior to the 24-hour reading of the challenge the test sites were depilated.

APPENDIX E

SUMMARY TABLE OF STUDY INFORMATION AND RESULTS

Test item identification: Name: TKA 40254 (CGX RU 997) Batch No.: 02/2001			SUMMARY TABLE		
SKIN TOLERANCE STUDIES / IMMUNOSTIMULATION (sensitization potential by intradermal and epidermal administration) **Maximization Test (M&K Test)**			RCC Study No.: 841900 Study Completion Date: 07-JUN-2002		
Species/Strain: Ibm: GOHI; SPF-quality guinea pigs (synonym: Himalayan spotted)			Number of exp. animals: 15		
Procedure	Administration route/site		Day	Vehicle	
First induction	Intradermal/scapular		1	Test: 1. FCA:phys. saline 1:1 2. PEG 300 3. FCA:phys. saline 1:1 Control: 1. FCA:phys. saline 1:1 2. PEG 300 3. FCA:phys. saline 1:1 / PEG 300 50/50	
Second induction Challenge	Epidermal occl./scapular Epidermal occl./left flank		8 22	} PEG 300	
Study group	Control group		Test group		
	Application	No. of appl. and dose/animal	Concentration of test item	No. of appl. and dose/animal	
Intradermal induction 1.	FCA:phys. saline 1:1	2x100 µl/i.d.	0 %	2x100 µl/i.d.	
2.	PEG 300	2x100 µl/i.d.	25 %	2x100 µl/i.d.	
3.	FCA:phys. saline 1:1/PEG 300 50/50	2x100 µl/i.d.	25 %	2x100 µl/i.d.	
Epidermal occl. patch induction	PEG 300	Saturated patch/8 cm^2	100 %	Saturated patch/8 cm^2	
Challenge A	25 %	} Saturated patch/9 cm^2	25 %	} Saturated patch/9 cm^2	
B	PEG 300		PEG 300		
No.of animals & Sex	5 females		10 females		
Animals with skin reactions / out of total					
Challenge A (24-hour reading)	0 / 5		10 / 10		
B	0 / 5		0 / 10		
Challenge A (48-hour reading)	0 / 5		9 / 9*		
B	0 / 5		0 / 9		
Summary of salient findings: The test item tested under the described conditions is considered to be an extreme skin sensitizer.					
Study in compliance with GLP: yes [X] no [ ]			QA inspected/audited: yes [X] no [ ]		

* One animal of the test group was found dead on test day 25.

A = left flank B = right flank

APPENDIX F

CERTIFICATION

- ACCREDITATION / EUROPEAN STANDARD EN 45001

- GLP – CERTIFICATION

Eidgenössisches Amt für Messwesen
Office fédéral de métrologie
Ufficio federale di metrologia
Swiss Federal Office of Metrology

S Schweizerische Akkreditierungsstelle
A Service d'accréditation suisse
S Servizio d'accreditamento svizzero
S Swiss Accreditation Service

ACCREDITATION

Based on the Accreditation and Designation Ordinance
dated 17th June 1996
the Swiss Federal Office of Metrology grants the

RCC Ltd
Toxicology Division
Zelgliweg 1
4452 Itingen

accreditation as a

Testing Laboratory for toxicological investigation of pharmaceuticals and medical devices, agrochemicals, industrial chemicals, food- and feed-additives

in accordance with SN EN 45001.

The accredited scope of testing is defined in the Official Directory of the Accredited Testing Laboratories in Switzerland. The relevant requirements of the ISO 9002 standard are also covered by this accreditation.

Accreditation number: STS 085

Date of the accreditation: 16th September 1994
Date of the last renewal of the accreditation: 20th September 1999
The accreditation is valid until: 19th September 2004

Wabern, 20th September 1999

Swiss Federal Office of Metrology
The Director — Dr Wolfgang Schwitz

The head of SAS — Hanspeter Ischi

SAS is a signatory of the multilateral agreements of the European co-operation for Accreditation (EA) for calibration, testing and certification of products, personnel, quality and environmental management systems.

The Swiss GLP Monitoring Authorities

Swiss Federal Office of Public Health

Swiss Agency for the Environment, Forests and Landscape

Intercantonal Office for the Control of Medicines

Statement of GLP Compliance

It is hereby confirmed that

during the period of

August 15 – 17, 2000

the following Test Facilities of

RCC Ltd
4452 Itingen
Switzerland

were inspected by the Federal Office of Public Health, the Swiss Agency for the Environment, Forests and Landscape and the Intercantonal Office for the Control of Medicines with respect to the compliance with the Swiss legislation on Good Laboratory Practice.

Test Facilities	**areas of expertise***
- Toxicology Division	**TOX, ACC**
- Environmental Chemistry and Pharmanalytics Division	**ACC, ECT, ENF, PCT,RES, OTH (Animal metabolism)**
- Microbiological Diagnostics by Biotechnology & Animal Breeding Division	**OTH (Microbiology)**

The inspection was performed in agreement with the OECD Guidelines for National GLP Inspections and Audits. It was found that the aforementioned test facilities were operating in compliance with the Swiss Ordinance relating to Good Laboratory Practice [RS 813.016.5] at the time they were inspected.

Federal Office of Public Health
The Director

Bern, November 2000

Prof. Th. Zeltner

* TOX = Toxicology ; ACC = Analytical and Clinical Chemistry ; ECT = Environmental toxicity on aquatic and terrestrial organisms ; ENF = Behaviour in water, soil and air. Bioaccumulation ; PCT = Physical-chemical testing ; RES = Residue studies ; OTH = Other, to be specified.